Stiffness Is the Cardinal Symptom of Inflammatory Musculoskeletal Diseases, Yet Still Variably Measured: Report from the OMERACT 2016 Stiffness Special Interest Group


ABSTRACT. Objective. The objectives of the Outcome Measures in Rheumatology (OMERACT) Stiffness special interest group (SIG) are to characterize stiffness as an outcome in rheumatic disease and to identify and validate a stiffness patient-reported outcome (PRO) in rheumatology.

Methods. At OMERACT 2016, international groups presented and discussed results of several concurrent research projects on stiffness: a literature review of rheumatoid arthritis (RA) stiffness PRO measures, a qualitative investigation into the RA and polymyalgia rheumatica patient perspective of stiffness, data-driven stiffness conceptual model development, development and testing of an RA stiffness PRO measure, and a quantitative work testing stiffness items in patients with RA and psoriatic arthritis.

Results. The literature review identified 52 individual stiffness PRO measures assessing morning or early morning stiffness severity/intensity or duration. Items were heterogeneous, had little or inconsistent psychometric property evidence, and did not appear to have been developed according to the PRO development guidelines. A poor match between current stiffness PRO and the conceptual model identifying the RA patient experience of stiffness was identified, highlighting a major flaw in PRO selection according to the OMERACT filter 2.0.

Conclusion. Discussions within the Stiffness SIG highlighted the importance of further research on stiffness and defined a research agenda. (First Release December 15 2016; J Rheumatol 2017;44:1904–10; doi:10.3899/jrheum.161073)
Stiffness affects 70%–75% of people with rheumatoid arthritis (RA) regardless of treatment status and 44%–80% of patients in low disease activity. Evidence shows that stiffness is important to patients with RA in flare and remission states, and it is an integral part of the RA experience. Stiffness adversely affects health-related quality of life and is associated with an earlier initiation of disease-modifying therapy in RA.

Further, stiffness is a key symptom recognized by patients and clinicians in many other inflammatory rheumatic diseases including polymyalgia rheumatica (PMR) and psoriatic arthritis (PsA) among others. In RA, stiffness assessment is particularly relevant because it likely influences patients’ ability to meet remission criteria. A systematic review in RA low disease activity and remission identified and summarized the measurement properties of currently available stiffness patient-reported outcome (PRO) measures. The review identified only 2 articles, which made conflicting recommendations about the most appropriate concept for stiffness assessment (morning stiffness duration or severity), and concluded that there was insufficient scientific data supporting current stiffness measures.

The aims of the OMERACT 2016 stiffness special interest group (SIG) were to consolidate the work on stiffness across inflammatory rheumatic conditions to systematize future research on the topic and to work toward identifying and validating an outcome measure for stiffness in rheumatic diseases that would be consistent with the methodology outlined by the OMERACT filter. In preparation for the Stiffness SIG at OMERACT 2016, the following research projects were conducted: (1) a literature review of stiffness PRO measure in RA, (2) a synthesis of qualitative research conducted in RA, (3) qualitative research with patients with PMR, (4) the development, refinement, and testing of candidate items for an RA stiffness questionnaire, and (5) the examination of stiffness items in RA and PsA.

Stiffness Literature Review
A literature review was conducted to identify and assess measurement properties of stiffness PRO in RA. The search was conducted in PubMed using a validated search filter and was consistent with a prior systematic literature review in RA remission, including articles identified there. Article screening determined 25 articles suitable for full-text review (Figure 1). From these, 52 individual stiffness PRO measures were identified. All but 1 assessed morning stiffness or early morning stiffness. Most assessed the concepts of duration (n = 30) or severity/intensity (n = 18), while others assessed improvement (n = 1), importance (n = 1), and 2 were unclear. There was great variation in PRO wording, response options, format, and time frame. For example, PRO item formats included visual analog scale (VAS; n = 14), numeric rating scale (NRS; n = 5), Likert scale (n = 7), and minutes in free text (n = 23); 2 items were unclear. Items were also poorly defined with 22 items unclear regarding some or all item components. Reports of face, content, criterion and construct validity, reliability, and responsiveness were limited and inconsistent. Overall, severity items appeared to perform better than duration items in relation to construct validity and discrimination between disease states, responsiveness, and sensitivity to change, but evidence was limited. No articles reported the face or content validity of stiffness items and no patient involvement in item development was reported. A summary of the literature review findings is outlined in Table 1 and 2. Current RA stiffness assessment is heterogeneous, incompletely reported, and does not appear to have been developed according to the PRO development guidelines recommending incorporating the patient perspective.

Qualitative Investigation of Stiffness in RA
A synthesis of qualitative work identifying the RA patient experience of stiffness was performed by an experienced qualitative researcher. The published papers reviewed reported 2 independent conceptual models based on inductive thematic analysis of international focus groups and semistructured interviews. The synthesis identified 6 common domains (Figure 2). Patients considered stiffness a normal part of RA that was widely variable (in timing, duration, and location) and did not occur exclusively in the mornings. Stiffness was related to other RA symptoms, affected daily life, and was influenced by external or personal factors (e.g., medication, self-management). The key, common concepts that stiffness is not purely a morning symptom and is best evaluated by its effect with current stiffness assessments that focus on morning stiffness severity or duration. This indicates a poor match between the conceptual model and currently used PRO, a major flaw according to the OMERACT filter 2.0 recommendations for selecting PRO.

Qualitative Investigation of Stiffness in PMR
Qualitative research was conducted in PMR to investigate the
patient experience of stiffness and its assessment through 8 focus groups. The conceptual model of the PMR patient experience of stiffness had 4 major themes: symptoms, functional effect, influence on daily schedule, and approaches to measurement. Stiffness was an important symptom for patients, distinct from pain, and for some it was overwhelming and imposed restrictions on activities of daily life. For stiffness assessment, patients preferred an NRS or an assessment of stiffness effect on daily life functioning rather than a VAS. Findings in PMR are consistent with qualitative work performed in RA. Assessing functional effect may be a pragmatic approach to difficulties with current stiffness assessments.

Development of New RA Stiffness Questionnaire
A new PRO for stiffness in RA has been developed based on qualitative research findings, a qualitative investigation into the patient perspective of stiffness assessment, and an iterative process of item development involving clinicians, researchers, and patients. Cognitive interviews with patients with RA refined draft items into a set of 45 preliminary stiffness items. These were administered by a postal survey with additional PRO (patient’s global assessment (PtGA), VAS, pain NRS, Bristol Rheumatoid Arthritis Fatigue Severity NRS, flare question from the Preliminary Flare Questionnaire, modified Health Assessment Questionnaire (mHAQ), patient-based disease activity score) and demographic questions to a new sample of patients with RA (n = 277; 32.9% men; mean (SD) age 63.9 (12.4) yrs, range 23–97; median disease duration (interquartile range) 6 (3–15) yrs, range 1–45]. Successive rounds of analytical refinement were performed using principal component analysis and Cronbach’s alpha coefficient for internal consistency to identify the smallest number of informative items. This resulted in the development of a new RA stiffness PRO measure (RAST) with 21 items and 3 components identifying stiffness severity, physical effect, and psychosocial effect. The RAST PRO measure can now be tested in independent longitudinal studies to accumulate evidence on psychometric properties in RA and other rheumatic diseases.

Quantitative Testing of Stiffness Items in RA and PsA
Stiffness items (severity, duration, and effect) were assessed in a cross-sectional study of patients with PsA and age- and sex-matched RA controls in the Australian Rheumatology Association Database, a voluntary national registry for patients with inflammatory arthritis. Stiffness items and additional PRO (mHAQ, pain, PtGA) were completed electronically by 103/158 patients with PsA and 111/158 with RA. Ratings of stiffness severity, duration, and effect were comparable in RA and PsA. There was a high degree of correlation between different dimensions of stiffness (r = 0.71–0.89) and stiffness item formats (r = 0.58–0.90). Stiffness was independently associated with physical function in the multiple regression model. Stiffness severity and effect were most strongly associated with physical function (adjusted $R^2 = 0.60$).
A | B | C | D
---|---|---|---
1. Study Instrument Concept (1) Severity of MS (2) Severity of MS (3) Severity of MS (4) Duration of MS | Stem Wording (1) EWU (2) EWU (3) EWU (4) How long did it take for your stiffness to begin to ease after you got out of bed this morning? | Response Options/anchors (1) 10-cm VAS, no to very severe (2) 11-point NRS, no to very severe (3) 5-point VS, no, mild, moderate, severe, very severe (4) Mins
2. Rhind, et al (1) Severity of MS (2) Severity of MS (3) Duration of MS (4) Duration of MS | (1) EWU (2) EWU (3) How long does your MS last until it begins to improve? (4) How long does your MS last until maximum improvement occurs? | (1) 10-cm VAS, no to very severe (2) 11-point NRS, no to very severe (3) Mins (4) Mins
3. Hazes, et al (1) Duration of MS | (1) Waking to first improvement (2) Getting up to first improvement (3) Waking to maximum improvement (4) Getting up to maximum improvement (5) Waking to complete disappearance (6) Getting up to complete disappearance | (1) Mins (2) Mins (3) Mins (4) Mins (5) Mins (6) Mins
4. Ward (1) Duration of MS | (1) EWU | (1) Mins
5. Leeb, et al (1) Daily MS severity | (1) EWU | (1) 100-mm VAS, no to unbearable (2) Starting stiffness after a time of rest, EWU (3) EWU | (2) 100-mm VAS, no to unbearable (3) Mins
6. Yazici, et al (1) Duration of MS | (1) EWU | (1) 0 min, < 30 mins, 30 min to 1 h, 1–2 h, 2–4 h, > 4 h in all day, all day | (2) Mins, cutoff at 240
7. Westhoff, et al (1) Severity of MS | (1) EWU | (1) 0 min, 1–15 mins, 16–59 mins, ≥ 60 mins | (2) Mins, no to extremely severe
8. Khan, et al (1) Duration of MS | (1) From time of waking to time of max improvement | (1) 0 min, 1–30 mins, 31–60 mins, ≥ 60 mins | (2) Mins
9. El Miedany, et al (1) Duration of MS | (1) Over the last week when you awoke in the morning, did you feel stiff? Please indicate the number of minutes, or hours until you feel limber as you will be for the day. | (1) Mins, as time from awakening
10. Wiesinger, et al (1) Duration of MS | (1) EWU | (1) 10-cm VAS, anchors unclear | (2) EWU
11. Jastrząbek, et al (1) Duration of MS | (1) EWU | (1) Mins | (2) Duration of MS
12. Lie, et al (1) Duration of MS | (1) EWU | (1) Mins | (2) How would you describe the overall level of morning stiffness you have had from the time you wake up? (3) Duration of MS
13. Bykerk, et al (1) Severity of MS | (1) EWU | (1) 10-cm VAS, none to very severe (2) 10-cm VAS, 0 = 0 h to 10 = > 2 h | (2) Response options unclear (3) Stiffness severity
14. Hamad, et al (1) Duration of MS | (1) EWU | (1) 11-point NRS, anchors unclear | (2) Duration of MS
15. Bartlett, et al (1) Stiffness | (1) EWU | (1) Stiffness, EWU | (2) Duration of MS
16. | | | |
DISCUSSION

Stiffness is an important symptom for patients across rheumatic conditions. It has been included in the RA Flare core domain set since 2014, and its inclusion in the PMR core domain set and the research agenda for PsA was endorsed at OMERACT 2016. Qualitative research and literature reviews demonstrate that current stiffness PRO may not adequately reflect stiffness dimensions that matter most to patients.\(^2,4,5,8\) Hence, current stiffness items do not meet the OMERACT filter 2.0 “eyeball test” of being a good match with the domain of interest.\(^46\) Discussions within the SIG suggested that while stiffness is a generalizable domain across several rheumatic conditions, notable differences exist in the patient experience. For example, patients within the SIG highlighted that the location of stiffness would differ between PMR and RA and this should be reflected in the wording of items. This is also relevant in ankylosing spondylitis or PsA with axial spondyloarthritis. Possible solutions could include further qualitative investigations with different patient groups to tailor assessments to specific populations, or design a comprehensive databank of stiffness items that can be administered using an interactive approach such as computer-adaptive testing. Meanwhile, research to develop and validate a comprehensive RA stiffness PRO measure is currently ongoing in the United Kingdom, United States, and Australia. This work has been grounded on qualitative research with patients and followed by item testing and refinement. Further testing and refinement in independent RA cohorts and additional rheumatic diseases is ongoing.

Table 1. Continued.

<table>
<thead>
<tr>
<th>Study</th>
<th>Instrument Concept</th>
<th>Stem Wording</th>
<th>Response Options/anchors</th>
</tr>
</thead>
<tbody>
<tr>
<td>van Nies, et al</td>
<td>(1) Duration of MS</td>
<td>(1) Do you experience stiffness when you get up in the morning? If so, for how many minutes?</td>
<td>(1) Mins, &lt; 60 or ≥ 60 and ≥ 30 or ≥ 90</td>
</tr>
<tr>
<td></td>
<td>(2) Duration of MS</td>
<td>(2) Do you experience morning stiffness? If yes, for how long?</td>
<td>(2) Mins, &lt; 60 or ≥ 60 and ≥ 30 or ≥ 90</td>
</tr>
<tr>
<td></td>
<td>(3) Duration of MS</td>
<td>(3) Do you experience stiffness in your joints in the morning? And if so, how long does this stiffness endure?</td>
<td>(3) Mins, &lt; 60 or ≥ 60 and ≥ 30 or ≥ 90</td>
</tr>
<tr>
<td></td>
<td>(4) Severity of MS</td>
<td></td>
<td>(4) 100-mm VAS, mild 0–33, moderate 34–67, severe 68–100</td>
</tr>
<tr>
<td>Ward, et al</td>
<td>(1) Severity of MS</td>
<td>(1) EWU</td>
<td>(1) 100-mm VAS, none to very severe</td>
</tr>
<tr>
<td></td>
<td>(2) MS transition</td>
<td>(2) Since the start of the study, my stiffness in the morning has...</td>
<td>(2) 3-point VS, improved, stayed the same, worsened</td>
</tr>
<tr>
<td></td>
<td>(3) MS transition</td>
<td>(3) MS transition importance, EWU</td>
<td>(3) 7-point VS, hardly important at all to extremely important</td>
</tr>
<tr>
<td>Ward, et al</td>
<td>(1) Severity of MS</td>
<td>(1) EWU</td>
<td>(1) 100-mm VAS, none to severe</td>
</tr>
<tr>
<td></td>
<td>(2) Duration of MS</td>
<td>(2) How long does your MS last until maximum improvement occurs?</td>
<td>(2) Mins</td>
</tr>
</tbody>
</table>

* Different cohorts used different questions. PRO: patient-reported outcome; MS: morning stiffness; EMS: early morning stiffness; EWU: exact wording unclear; VAS: visual analog scale; NRS: numerical rating scale; VS: verbal scale.

Figure 2. Synthesis of patient-derived conceptual models of stiffness in RA. RA: rheumatoid arthritis.
Research Agenda

The OMERACT 2016 Stiffness SIG defined the following items on its research agenda: (1) investigation of contextual factors and adverse events that can be achieved through secondary data analysis of 2 qualitative datasets we collected in RA, a PMR qualitative dataset, as well as additional qualitative datasets (PsA), (2) a qualitative investigation into the patient perspective of stiffness assessment in rheumatic diseases other than RA and PMR, (3) development and validation of stiffness assessment tools in RA, which may include further psychometric evaluations of the RAST and testing using item response theory, (4) an investigation into stiffness pathophysiology across rheumatic conditions, and (5) a review of stiffness assessment in osteoarthritis and nonrheumatic conditions to assess potential for integration with rheumatic disease stiffness.

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REFERENCES


